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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,668	01/06/2006	Stephen Robert Wedge	056291-5229	1521

9629 7590 12/24/2008
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1614	
MAIL DATE	**DELIVERY MODE**
12/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,668	WEDGE ET AL.	
	Examiner	**Art Unit**	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _17 September 2008_.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _10 and 12-20_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _10 and 12-20_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _09/17/2008_.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Claims 10 and 12-20 are pending. Receipt and consideration of Applicants' amended claim set and remarks/arguments mailed on 09/17/2008 is acknowledged. Claims 1-9 and 11 is cancelled, claims 12 and 13 are amended and new claims 14-20 were added.

Applicants' arguments, filed 09/17/2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112- I st Paragraph: Enablement

This rejection is necessitated by the newly submitted claims filed on 09/17/2008.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating human lung cancer and other solid tumors, does not reasonably provide enablement for “treatment of cancer” as recited in instant claims 12 and 13. Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims..

The test of enablement requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described by the court In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Wands states on page 1404,

" Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman, They include (1) The breadth of the claims; (2) The nature of the invention (3) The state of the prior art (4) The level of ordinary skill; (5) the level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention on the content of the disclosure.

The Wands factors are relevant to the instant fact situation for the following reasons:

When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to methods of treating cancer by administering to a mammal in need thereof an effective amount of combination of VEGFR inhibitor ZD6474 and at cisplatin.

(2) The state of the prior art

With respect to cancer, this a broad term which encompasses numerous forms of neoplastic diseases, each involving different types of tissues and organs and also includes blood-borne diseases. As recognized in the art, many different anti-neoplastic drugs are used to treat a variety of cancers, but there is no one drug or one drug combination, which is capable of treating all cancers in general. Please see pages 1226-1229 of Goodman & Gilman's.

(3) The relative skill of those in the art

The relative skill of those in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular anticancer agent or combination of agents that is effective against all cancer cell types.

(4) The nature of the invention, and the predictability or unpredictability of the art

The nature of basic science of oncology is highly unpredictable in that a there is no one particular agent or combination of agents known to be effective for the treatment of one specific kind of cancer and treatment options depend on the state and progression of the cancer. This unpredictability increases when trying to treat a broad spectrum of cancers. Additionally, testing functions that are related to particular cancer can be misleading because controlled environment in vitro cannot predict the effect of the drug in vivo. The unpredictable nature of cancer assays has long been recognized. See, e.g., Gura (Science, vol. 278, pp. 1041-1042 (1997)) and Booth (Nature's Review, Drug discovery, Vol 2, pp. 609-610 (2003) which provides an overview of the problems involved with sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile. Gura notes in 2nd paragraph of his article that

since formal screening in 1955 many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy. As noted therein, the "fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." The reasons are many, including basic differences between human patients on the one hand, and animal and cell culture models on the other (third paragraph of the article).

According to Booth (2^{nd} paragraph, pp. 609) even though more than 500 oncology compounds are in development, only a few achieve regulatory approval each year and there are only ~90 approved oncology drugs in the US today. As noted therein the "early development trials do not seem to very predictive of success rates for later developments. Booth details the scientific and regulatory challenges associated with developing anti-cancer drug (4^{th} paragraph, pp. 609) . An efficient means of predicting activity with in vivo models remains desirable for compounds with anti-proliferative activity in vitro to this day. Accordingly, the unpredictability of the pharmaceutical and cancer art is high. Additionally, the lack of significant guidance from the present specification or prior art with regard to the actual treatment of all cancer cell types in a mammal, including a human, with the claimed compounds as the active ingredients makes practicing the claimed method unpredictable.

(5) The breadth of the claims

The complex nature of the subject matter to which the present claims are directed is exacerbated by the breadth of the claim. The claims are broad and encompass treatment of a vast number of possible cancer types including blood-borne

tumors. Finally, to the extent that the term "treatment" indicates inhibiting further development or causing the regression of a disease, i.e. cancer, such is not enabled for the breadth of the claims; which encompass all cancers in general.

(6) The amount of direction or guidance presented

The specification of the instant application provides little guidance in terms of treating patients comprising the administration of ZD6474 and platinum anti cancer agent with ionizing radiation for the purposes of treatment of cancer. In view of the unpredictable nature of treating cancer and angiogenesis in general and the lack of correlation between in vitro experimentation and in vivo predictability, the lone working example is insufficient to guide or teach one of skill in the art how to use the instant invention.

(7) The presence or absence of working examples

The specification provides a single working example of administering ZD6474 (25-75 mg/m2 orally (p.o.) with cisplatin (4 mg/kg intraperitoneally (i.p.)) or a combination thereof to human tumor cells of human lung cancer (NSCLC) xenograft model (see specification page 14, lines 10 to page 15 line 6).

(8) The quantity of experimentation necessary

Since (1) the prior art recognizes that no one compound or combination of compounds is capable of treating the vast number of possible cancerous diseases encompassed by the term "cancer"; (2) the specification provides guidance and working examples for only one type of cancer i.e. lung cancer and lacks a representative number of working examples of cancers that would be treated by the claimed combinations and (3) since

the claims are very broad and include treatment of any type of cancer including blood-borne cancers, one of ordinary skill in the art would be burdened with undue experimentation to determine which cancers would be treated by administration of the claimed active agents.

Claim Rejections - 35 USC § 103

This rejection is necessitated by the newly submitted claims filed on 09/17/2008.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-20 are rejected under 35 U.S.C 103 (a) as being unpatentable over Hennequin et. al (WO 01/32651, IDS reference) in view of Kuenen et al (Journal of Clinical Oncology, vol. 20, pp 1657-1667 (March 2002) and Gorski et al (Cancer Research, vol. 59, pp. 3374-3378 (July 1999, referenced in IDS) as evidenced by Desoize et al (Critical Reviews in Oncology/hematology, 42 (2002)317-325).

Claims 12 and 13 has been amended to recite a method for the treatment of cancer by administering ZD6474 with a platinum anti-tumor agent and/or with ionizing radiation. New claims 14-20 are dependent on currently amended claim 12 or 13 and add further limitations as to the type of platinum anti-tumor agent and the type of cancer to be treated.

Hennequin et al discloses the use of ZD6474 specifically identified as a compound of formula 1(claim 8). Hennequin teaches that the compounds of his invention possess very good inhibitory activity against t VEGF receptor tyrosine kinase, show *in vivo* activity against a range of tumor xenografts in mice an possess a beneficial toxicology profile when tested over 14 days in rats (page 2,lines 20-24. Hennequin also teaches that the compounds of formula 1 have antiangiogenic and/or vascular permeability reducing effects which make them useful in a wider range of diseases

states such as cancer, particularly to slow the growth of primary and recurrent solid tumors of, for example, the colon, breast, lungs and skin and additionally the compounds of his invention are expected to inhibit the growth of those primary and recurrent solid tumors dependent on VEGF for their growth and spread and also those tumors which are dependent on EGF for their growth and spread (page 28, lines 5-21). Hennequin also teaches a pharmaceutical composition which comprises the compound ZD6474 in association with a pharmaceutically acceptable excepient or carrier (page 25, lines 7-10, claim 11). Hennequin further teaches that the treatment could be a sole therapy or may involve, in addition to a compound of the invention one or more other substance and/or treatments used simultaneously, sequentially or by separate administration of the individual components of the treatment (p 26, lines 22-31) and suggests the use of radiotherapy (p 26, line 30) and platinum derivatives (for example cisplatin, carboplatin) in combination with ZD6474 as conjoint treatment in the field of oncology (p 27, lines 24-25) . Finally, Hennequin demonstrates the activity of the compounds of formula I which includes ZD6474 in vivo on CaLu-6 tumor xenografts (lung carcinoma model) (page 22, lines 14-30).

Hennequin do not specifically teach a method of ZD6474 with platinum derivatives and specifically the use of ZD6474 with ionizing treatment.

However, Kuenen et al. teaches the use of cisplatin and SU5416 in patients with solid tumors. SU5416 is also a small molecule VEGF receptor inhibitor similar in its mechanism of action to ZD6474. Kuenen additionally teaches the advantages of combining angiogenesis inhibitor with chemotherapy (page 1658, paragraph 2). In their

study Kuenen et al. observed a higher incidence of thromboembolic and vascular events, however Kuenen et al reports that the vascular effects may be particularly related to the regimen tested in their phase I study and they did not attempt to reduce the dose of the chemotherapeutic drugs (page 1665, right col., 4th paragraph). The instant claims recite methods and compositions for treating solid cancerous tumors comprising administering ZD6474 and platinum anti-tumor agents. It is noted that the "comprising" language of the instant claims is open language that does not preclude the addition of other therapeutically active agents. Please see M.P.E.P. 2111.03.

Gorski et al teaches that VEGF inhibitors, a class of compounds of which ZD6474 is a member, administered with ionizing radiation (IR) results in greater than additive anti-tumor effects. Gorski teaches that ionizing radiation is a major therapeutic modality that is primarily effective in the treatment of small tumors, whereas large tumors respond only with considerable toxicity to normal tissues. Gorski's study demonstrates that ionizing radiation can induce VEGF expression and that this VEGF induction may represent a tumor response to radiation stress, Therefore, blocking the effects of VEGF production by irradiated Lewis Lung carcinoma and human tumor xenografts results in greater than additive antitumor effects in vivo for very large experimental tumors. Gorski further teaches that blocking the action of VEFG in addition increases IR-induced killing since VEFG abrogates the killing of endothelial cells by IR (page 3378, paragraph1).

With regards to the limitation set forth in instant claim 16, wherein the platinum anti-tumor agent is oxaliplatin. Hennequin and Kuenen suggest combining cisplatin and

carboplatin with the ZD6474 or antiangiogenic drug. Oxaliplatin is a functional equivalent of cisplatin and carboplatin and is encompassed by the broad category of platinum anti-tumor compounds as evidenced by Desoize et al. Desoize et al. teaches that the mechanism of action of cisplatin, carboplatin and oxaliplatin are similar in that they all are pro-drugs which form adducts with DNA, impairing DNA synthesis and repair (Abstract, Page 317), Accordingly, one of ordinary skill in the art would be motivated to replace cisplatin or carboplatin with its functional equivalent oxailplatin when conducting the structural activity relationship of the ZD6474 with a platinum anti-tumor compounds.

With regards to limitation set forth in instant claim 19 about treatment of colorectal cancer, Hennequin also teaches that the compounds of formula 1 which include ZD6474 have antiangiogenic and/or vascular permeability reducing effects which make them useful in a wider range of diseases states such as cancer, particularly to slow the growth of primary and recurrent solid tumors of, for example, the colon, breast, lungs and skin. Accordingly, it would be obvious to one of ordinary skill in the art to also treatment of colorectal cancer with the instantly claimed combination as it belongs to the solid tumor category taught by Hennequin.

In view of the forgoing references, it would have been prima facie obvious to one of ordinary skill in the art to combine ZD6474 with a platinum anti-tumor agent such as cisplatin or ionizing agents to develop a method of treating solid cancers. Hennequin teaches the method of treating solid cancers by administering the instantly claimed compound ZD6474 and suggests that it can be combined with a platinum anti-tumor

drug or ionizing radiation in the treatment protocol. Kuenen suggests the combination of cisplatin with another VEGF inhibitor SU5416 which is a functional equivalent of ZD6474 and gemcitabine for treatment of solid tumors and Gorki suggests the combination of VEGF inhibitors to be administered along with ionizing radiation to improve the therapeutic effect of radiation. Accordingly, an ordinarily skilled artisan would be motivated to develop a method and a composition for the treatment of solid tumors using ZD6474 with concurrent radiotherapy and platinum derivatives (a well known anti-cancer drugs) to use in the treatment of cancer at the time of the instantly claimed invention thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

Furthermore, combining ZD6474 with platinum anti-tumor agent into composition would have been obvious to one of ordinary skill in the art at the time of invention, since they are both known chemotherapeutic agents. Applicant is reminded of *In re Kerkhoven*, which affirmed that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....the idea of combining them flows logically from their having been individually taught in the prior art". *In re Kerkhoven*, 626 F .2d 846, 850, 205, USPQ 1069, 1072 (CCPA 1980). The addition of a pharmaceutically acceptable carrier or excepient to the aforementioned pharmaceutical composition would have been obvious to one of ordinary skill in the art at the time of the invention and they would be motivated to do so to allow for effective administration to the patient and delivery to the targeted tissue.

One of ordinary skill in the art would have been motivated to do the above in order to develop a more powerful cancer treatment method than existing ones. One of ordinary skill in the art would have a reasonable expectation of success since each of the components has been shown to have their own anti-tumor activity and suggestions of combination are provided by the prior art.

Rejection of Instant claim 10 under 35 U.S.C 103 (a) as being unpatentable over Hannequin et. al (WO 01/32651, IDS reference) in view of Kuenen et al (Journal of Clinical Oncology, Vol 20, pp 1657-1667 (March 2002) and Gorski et al (Cancer Research, Vol 59, pp. 3374-3378, July 1999, referenced in the IDS) is maintained for reasons of record restated below.

Hennequin et al discloses the use of ZD6474 specifically identified as a compound of formula 1(claim 8) and teaches the use of this compound or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-angiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human (p.26, lines 6-10; claim 12-13). Hannequin further teaches that the treatment could be a sole therapy or may involve, in addition to a compound of the invention one or more other substance and/or treatments used simultaneously, sequentially or by separate administration of the individual components of the treatment (p 26, lines 22-31) and suggests the use of radiotherapy (p 26, line 30) and platinum derivatives (for example cisplatin, carboplatin) in combination with ZD6474 as conjoint treatment in the field of oncology (p 27, lines 24-25)

Hannequin does not however teach the specific use of ZD6474 with platinum derivatives. This deficiency is cured by teachings of Kuenen et al. who teaches the use of cisplatin and SU5416 in patients with solid tumors. SU5416 is also a small molecule VEGF receptor inhibitor similar in its mechanism of action to ZD6474. Kuenen additionally teaches the advantages of combining angiogenesis inhibitor with chemotherapy (page 1658, paragraph 2).

Hannequin does not teach the use of ZD6474 with ionizing treatment. This deficiency is cured by Gorki et al who teaches that VEGF inhibitors, a class of compounds of which ZD6474 is a member, administered with ionizing radiation results in greater than additive anti-tumor effects (page 3378, paragraph1)

Therefore it would have been obvious to one of ordinary skill in the art at the time of the instantly claimed invention to prepare a medicament using ZD6474 with concurrent radiotherapy and platinum derivatives (a well known anti-cancer drugs) to use in the treatment of cancer and in the production of an anti-angiogenic and/or vascular permeability reducing effect in a warm-blooded animal, thus resulting in the practice of the instantly claimed invention (Claims 1-6, 10-13) with a reasonable expectation of success.

Furthermore, combining ZD6474 with platinum anti-tumor agent into a pharmaceutical composition or kit (instant claims 10-11) would have been obvious to one of ordinary skill in the art at the time of invention, since they are both know chemotherapeutic agents. Applicant is reminded of *In re Kerkhoven*, which affirmed that "It is prima facie obvious to combine two compositions each of which is taught by the

prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....the idea of combining them flows logically from their having been individually taught in the prior art". *In re Kerkhoven*, 626 F .2d 846, 850, 205, USPQ 1069, 1072 (CCPA 1980). The addition of a pharmaceutically acceptable carrier or excepient to the aforementioned pharmaceutical composition would have been obvious to one of ordinary skill in the art at the time of the invention and they would be motivated to do so to allow for effective administration to the patient and delivery to the targeted tissue.

One of ordinary skill in the art would have been motivated to do the above in order to develop a more powerful cancer treatment method than existing ones. One of ordinary skill in the art would have a reasonable expectation of success since each of the components has been shown to have their own anti-tumor activity. Therefore the above references in combination render claims 1-6 and 10-13 prima facia obvious to one of ordinary skill in the art.

Response to Applicant's arguments filed on 09/17/2008

Examiner acknowledges Applicants' arguments in response filed on 09/17/2008.

In light of the new grounds of rejection above, the arguments submitted on 09/17/2008 which was for the previously submitted rejection is moot. However, since the examiner has used the same art as in the previous rejection, arguments which still apply to the art will be addressed.

Firstly, Applicants argue that there can be no basis to obtain the combination instantly claimed based on Hennequin, Kuenen and Gorski alone or in combination. Applicants base this argument on the fact that no single reference discloses ZD3474 in combination with platinum anti-tumor agent. However, the Examiner notes that the present rejection is an *obviousness* rejection, not an anticipation rejection. As such, the question is whether the subject matter, as a whole, would have been obvious to one of ordinary skill in the art at the time of the invention, not whether any given reference teaches all the limitations of the instant claims. Additionally the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). It is noted In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With respect to Applicant's argument that Hennequin's listing of "platinum derivatives" such as cisplatin and carboplatin which can be used in combination with ZD6474 is only a part of the overall discussion of such conjoint treatment, Examiner would like to draw Applicant's attention to the following:

"[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." Id. at 1742. Consistent with this reasoning, it would have obvious to have selected various combinations of various disclosed ingredients from within a prior art disclosure, to arrive at compositions "yielding no more than one would expect from such an arrangement". In this instance since the prior art teaches combination of ZD6474 or other VEGFR inhibitors with platinum anti-tumor drugs, it would have been obvious to one of ordinary skill in the art to select cisplatin or carboplatin in combination with ZD6474 to create a chemotherapeutic combination for treating cancer with at least additive anticancer efficacy.

Applicant's argument that Kuenen reference is teaching a three component combination of cisplatin + gemcitabine + Su5416. The instant claims recite methods and

compositions for treating cancer comprising administering ZD6474 with platinum anti-tumor agents. It is noted that the "comprising" language of the instant claims is open language that does not preclude the addition of other therapeutically active agents. Please see M.P.E.P. 2111.03. Irrespective of the starting point of therapy being comparison of the three components combination to combination of cisplatin/gemcitabine, Kuenen provides ample suggestion along with his reasoning in page 1658, paragraph 2, for one of ordinary skill in the art motivation to combine an anticancer agent such as cisplatin with a VEGF inhibitory agent. With respect to applicant's argument the Kuenen teaches away from such a combination due to the high incidence of vascular effects observed in the study, Examiner would like to point out to page 1665, 4th paragraph, where Kuenen et al state that ongoing studies of VEGFR inhibitors in combination with other drugs such as fluorouracil, fluorouracil/ irinotecan, carboplatin/paclitaxel and paclitaxel, no increased incidence in thromboembolic events have been reported, thus suggesting that the drug can be combined with other platinum anti-tumor agent such as carboplatin where no such vascular effects is observed. Furthermore Kuenen also teaches that the higher incidence of vascular events seen in their study may therefore be particularly related to the regimen tested in their phase I study. Kuenen also adds that they did not attempt to reduce the dose of the drugs, suggesting that decreasing the dosage concentration and altering the regimen may result in decreased or no vascular effects. Accordingly, when combined with the teachings of Hennequin, Kuenen provides motivation to one of ordinary skill in the art to develop a method of treating solid cancer by combining an

anti-VEGFR drug with a platinum anti-tumor drug, albeit the method have to be developed extensively in an in-vitro and in-vivo animal model testing before taking it on to clinical trials. If anything, Kuenen provides motivation to the ordinarily skilled artisan to ensure adequate in-vitro testing and in-vivo animal model testing to also evaluate potential vascular effects.

Applicants argue over the Gorski reference that the anti-VEGF antibody used in the reference has a different profile of activity, structure and different modes of actions than the instantly claimed ZD6474 drug. While agreeing with the Applicants, Examiner , irrespective of the mechanism of action the ultimate effect provided by both agents in a system is the same where in the VEGF is prevented from binding to the VEGF receptor. Both are targeting the VEGF signaling pathway. Additionally, the Gorski reference is used here for its teachings of improvement of the effects of ionizing radiation on tumor cells by blocking the induction of VEGF expression which suggests to one of ordinary skill in the art that combination of ionizing radiation treatment with an agent which inhibits VEGF receptor activation and/or release of VEGF into the endothelial cells would potentially be useful in enhancing the beneficial effects of ionizing radiation.

With regards to the Applicant's argument of unexpected results, Applicants data presented in the instant disclosure and the two references cited in the response of 09/17/2008 has been considered and found not persuasive.

The data disclosed by the applicant in figure 1 is with respect to lung cancer only and at specific concentrations of ZD6474 and cisplatin. In the combination therapy

utilized in this experiment, specific concentration of ZD6474 was first administered followed by specific concentration of cisplatin 2 hours later (page 14, line 23-24 of the instant disclosure). Figure 1 which shows the decrease in mean tumor volume with treatment, shows that the effect of combination of ZD6474 and cisplatin is less than additive. For example at 43 days post cell implant, inhibition of tumor volume with cisplatin alone brings down the tumor volume to 1.5 cm^3, inhibition of tumor volume with ZD6474 is approximately 1.0 cm^3, the combination of cisplatin and ZD6474 displayed tumor inhibition of approximately 0.75 cm^3, which is less than additive effect expected (approximately 0.5 cm^3). Accordingly, the data presented does not support unexpected results argued by the applicant and the experimental details are not commensurate with the full scope of what is claimed. For example, instant claim 12 is drawn towards the method of treatment of cancer which comprises administering to said animal ZD6474 **before, after or simultaneously** with an effective amount of a platinum anti-tumor agent, whereas the combination therapy of the allegedly unexpected results is provided apparently only simultaneously.

Unexpected results claimed by the applicants over the Morrelli et al reference is acknowledged but is not found to be persuasive. This study utilized KYSE30 esophageal squamous epithelial cancer cells. Chemotherapy protocol included treatment with the platinum compounds for 24 hours followed by ZD6474 treatment for three consecutive days. Reverse protocol was also tested as demonstrated in line 3 of Table 1. Again although synergy as calculated was observe with the first treatment protocol, antagonistic results were observed when the treatment procedure was

reversed to first treat with ZD6474 followed by platinum compounds (CI of 1.92, 1.74 and 1.68 for cisplatin, carboplatin and oxailplatin respectively). At the bottom of the legend under table 1 Morrelli discloses that CI greater then 1 is antagonism.

With regards to the data presented by Troani et al (2006) Molecular Cancer Therapeutics 5 (7) 1883-1894, cited by the applicant on page 11 of their response filed on 09/17/2008, examiner finds it unpersuasive and not commensurate to the scope of the instant claims. The experiment was conducted on colorectal cancer cells only at specific concentrations of oxailplatin and ZD6474. Examiner would like to point out the exact sequence of treatment of the combination is critical in achieving the synergy. Synergy is observed only when the treatment included exposure to oxailplatin for 24 hours followed by ZD6474 treatment for 48 hours. The reverse treatment and concurrent treatment were in fact antagonistic instead of synergistic effect. (page 1886, right column)

Accordingly, the exact concentration of the agents and the sequence of addition is very critical to achieve the synergistic effect observed in the above two studies. The sequence of addition and the specific time of exposure appear to be critical to achieve the synergistic effect observed. The instant claims do not recite these limitations required to achieve synergistic effect. For example, instant claim 12 is drawn towards the method of treatment of cancer which comprises administering to said animal ZD6474 **before, after or simultaneously** with an effective amount of a platinum anti-tumor agent. Therefore, the unexpected results observed in these studies are with very specific parameters and are therefore not commensurate with the full scope of what is

claimed and the data is not probative of nonobviousness of the full scope of the claims as discussed above.

Accordingly, the claims 10 are deemed properly rejected under 35 U.S.C 103 (a).

Conclusion

Claims 10, 12-20 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614